Individual-based Modeling of Microcarrier Cell Expansion: A Sensitivity Analysis

B. Smeets, T. Odenthal, H. Ramon, H. Van Oosterwyck
KU Leuven, MeBioS, Kasteelpark Arenberg 30, 3001 Heverlee
bart.smeets@biw.kuleuven.be

Introduction

Accurate control of cell fate in the earliest stages of in vitro cell culture is paramount in new tissue engineering strategies. Cell expansion on porous or non-porous microcarriers facilitates threedimensional cell growth while preventing necrosis due to mass transport limitations. Moreover, the introduction of these microbeads provides a way to control the mechanical microenvironment of the cells, which has been shown to be of great influence in promoting cell differentiation for bone and cartilage formation. In this study, we use individual-cell based models to investigate how the properties of the microcarriers influence the microenvironment which the cells feel. Moreover, we present a sensitivity analysis that hints to the model robustness for biological and process heterogeneity.

Materials and Methods

The individual-cell based model considers the cells as discrete objects that interact through mechanical forces. These forces can be cell-cell or cell-microcarrier contact forces but could also arise due to biological mechanisms such as cell proliferation. For each time step, the equation of motion of the cells is solved for an overdamped system to obtain the cell velocities. Subsequently, explicit Euler integration yields the cell positions at a given time. Important model parameters, such as Young's moduli and attraction constants are obtained from experimental measurements in literature.

Results

Simulations of cell expansion on microcarriers reveal that both compressive and tensile stresses are present. During proliferation, a strong increase in compressive stress can be expected when confluence is reached on the microcarrier. The sensitivity analysis reveals that one of the strongest influencing parameters on the mechanical stress distribution is cell-microcarrier adhesion, which can be influenced by modifying the properties of the chemical coating of the microbead.

Discussion

This study gives a proof of principle that theoretically, a large biological heterogeneity is not required to result in a strongly heterogeneous microenvironment. As cell behavior and cell fate are strongly influenced by the mechanical microenvironment, one can assume that a large phenotypical heterogeneity might occur purely due to spatial and mechanical phenomena.

Conclusion

We developed an individual-cell based model that provides an interesting theoretical platform for cell expansion on microcarriers. Simulations have revealed that a big heterogeneity of mechanical stresses can be expected and that these stresses will peak when the proliferating cells reach confluence. Finally, the microcarrier coating properties strongly influence the cell mechanical microenvironment.